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2017-04

Panduru , N M , Nistor , I , Groop , P-H , Van Biesen , W , Farrington , K & Covic , A 2017 , ' Considerations on glycaemic control in older and/or frail individuals with diabetes and advanced kidney disease ' , Nephrology, Dialysis, Transplantation , vol. 32 , no. 4 , pp. 591-597 . https://doi.org/10.1093/ndt/gfx021

http://hdl.handle.net/10138/235594
https://doi.org/10.1093/ndt/gfx021

unspecified
publishedVersion

Nephrol Dial Transplant (2017) 32: 591–597
doi: 10.1093/ndt/gfx021
Advance Access publication 13 March 2017

ndt
Nephrology Dialysis Transplantation

NDT Perspectives

Considerations on glycaemic control in older and/or frail individuals with diabetes and advanced kidney disease

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ABSTRACT

The increasing prevalence of chronic kidney disease (CKD) and diabetes over the last decade has resulted in increasing numbers of frail older patients with a combination of these conditions. Current treatment guidelines may not necessarily be relevant for such patients, who are mostly excluded from the trials upon which these recommendations are based. There is a paucity of data upon which to base the management of older patients with CKD. Nearly all current guidelines recommend less-tight glycaemic control for the older population, citing the lack of proven medium-term benefits and concerns about the high short-term risk of hypoglycaemia. However, reports from large landmark trials have shown potential benefits for both microvascular and macrovascular complications, though the relevance of these findings to this specific population is uncertain. The trials have also highlighted potential alternative explanations for the hazards of intensive glycaemic control. These include depression, low endogenous insulin reserve, low body mass index and side effects of the medication. Over the last few years, newer classes of hypoglycaemic drugs with a lower risk of hypoglycaemia have emerged. This article aims to present a balanced view of advantages and disadvantages of intense glycaemic control in this group of patients, which we hope will help the clinician and patient to come to an individualized management approach.

Keywords: chronic kidney disease, frail, glycaemic control, older

INTRODUCTION

Older individuals represent the fastest growing group of people worldwide [1, 2]. Along with this, the prevalence of type 2 diabetes has also increased and has emerged as a major health problem especially in older people [3]. Old age and diabetes are the two most important causes of decline in renal function [4]. In older individuals with chronic kidney disease (CKD) and diabetes, the risk of frailty is considerable [5]. Frailty can hereby be defined as a clinical syndrome in which three or more of the following criteria are present: unintentional weight loss (10 lbs in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity [6]. A major characteristic of the frailty diathesis is an increased susceptibility to functional decline, dependency and death with relatively minor clinical or psychosocial misadventures.

As a consequence a distinct, highly vulnerable, population is emerging—frail older patients with diabetes mellitus and CKD.

Management of these patients is often complex and specific evidence-based treatment guidelines are often lacking. A European multidisciplinary initiative recently identified and prioritized potential topics to be addressed for this population. This joint initiative of the European Renal Association–European Dialysis Transplant Association and the European Union Geriatric Medicine Society prioritized the development of guidance on interdisciplinary referral of older patients with CKD Stage 3b–5 and listed 'glycaemic control' as a topic of interest [7].

Decisions about the optimal degree of glycaemic control in frail older patients with diabetes and advanced kidney disease are often difficult. It is uncertain whether strict glycaemic control results in benefit or harm in this population, especially as clinical trials on glycaemic control have almost always excluded patients with advanced CKD and/or frailty [8]. Older age was not an exclusion criteria in most clinical trials, but the mean age of included patients was lower than 65 years old [9]. However, the ADVANCE trial was different in this regard, with a mean age of 66 years [10]. Observational studies suggested that, in patients with diabetes and more than 75 years old, an HbA_{1c} below 6.9% can be protective when compared with the general population [11]. However, if CKD is one of the comorbidities, then all-cause mortality can increase in the diabetes group from 37% up to 333%, dependent on the estimated glomerular filtration rate (eGFR) [11].

However, in patients over 75 years old with CKD (eGFR <60 mL/min/1.73 m^2) those with diabetes had higher hazard ratios for death than controls (1.02–3.33, depending on eGFR). Moreover, trials of strict glycaemic control using conventional anti-diabetic medication in the general population have failed to show any benefits on cardiovascular outcomes and mortality, with only a small gain for the outcome of microvascular disease. In addition, intensive glycaemic control did not reduce the development of end-stage renal disease (ESRD) or doubling of the serum creatinine [12]. Trials did, however, reveal increased mortality related to hypoglycaemia [13–15]. This increased risk of hypoglycaemia would seem to outweigh any possible benefit of stricter glycaemic control. There are other considerations. In advanced CKD some medications may accumulate, increasing the risk of adverse events and hypoglycaemia [16]. The HbA_{1c} values in people with advanced CKD can be misleading, as low HbA_{1c} values in this patient group may overestimate the quality of glycaemic control [17–19]. Conversely, one should keep in mind that uraemia itself can enhance glycation independent of capillary glucose readings [20]. Finally, frailty and old age are associated with a wide range of comorbidities, a variable degree of cognitive dysfunction and a decreased life expectancy [6, 21]. The net effect of these factors may be to tip the balance away from the potential for long-term benefit towards the likelihood of short-term harm.

In this review, we aim to consider the translation of data derived from randomized controlled trials in other populations to assist clinicians in the management of glycaemic control in frail older patients with diabetes and advanced CKD. There is a paucity of data related to glycaemic management and control of type 1 diabetes later in life. Data on management of type 2 diabetes cannot be extrapolated to this category of patients. Therefore, this current article only focuses on patients with type 2 diabetes.

WHAT ARE THE CURRENT RECOMMENDATIONS?

Current targets for glycaemic control in older and frail individuals

According to the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus recommendations for frail and older adults, individuals with limited life expectancy (1 year or less), should have less-stringent HbA_{1c} goals (7.5–8.0% or even slightly higher in certain patients) [22–24]. The angiotensin-converting-enzyme inhibitor (AACE/ACE) Diabetes Guidelines reinforced the recommendation for less stringent HbA_{1c} goals (7–8%) in patients with a high risk of hypoglycaemia, long-standing diabetes or limited life expectancy [25]. The International Diabetes Federation (IDF) global guideline recommendation is an HbA_{1c} target $>7\%$ for people with limited life expectancy [26]. The International Association of Gerontology and Geriatrics, the European Diabetes Working Party for Older People and the International Task Force of Experts in Diabetes have set the HbA_{1c} target range to between 7.0% and 7.5% in older people, though this might be even higher in cases of lack of functional independence [27]. Similarly, the American Geriatric Society recommends a target HbA_{1c} for older people of $<8.0\%$ [28]. The National Institute of Clinical Excellence guideline suggests that the HbA_{1c} target should be $<7.5\%$ for people with type 2 diabetes treated with insulin or triple oral medication [29].

For individuals with diabetes and advanced CKD, the Kidney Disease Outcomes Quality Initiative reinforced the ADA recommendations [16, 30]. However, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended an HbA_{1c} target $>7.0\%$ in individuals with comorbidities or limited life expectancy and with high risk of hypoglycaemia [31]. In the ADA/EASD position statement there is no specific recommendation for patients with advanced CKD, but for patients with a limited life expectancy or extensive comorbid conditions an HbA_{1c} between 7.5% and 8.0% or even higher is advocated [22]. Finally, the IDF global guideline suggested a target HbA_{1c} of 7.0–7.5% or higher in the presence of modifying factors such as vulnerability to hypoglycaemia or the presence of comorbidities [26].

Nephrology guidelines

The recent European Renal Best Practice Guideline on management of patients with diabetes with advanced CKD (http://www.european-renal-best-practice.org/content/erbp-official-documents) recommended against tighter glycaemic control if this results in severe hypoglycaemic episodes [32]. Vigilant attempts to tighten glycaemic control were considered reasonable only with the intention to lower HbA_{1c} when values are $>8.5\%$ [32]). Urinary incontinence with polyuria should alert the clinician to check for hyperglycaemia. Only if there is no evidence of hypoglycaemia and HbA_{1c} is $>7\%$ should clinicians try to intensify treatment, though careful consideration of age and comorbidities is mandatory.

Hence, all current guidelines agree that in older people, especially those with comorbidities such as advanced CKD, glycaemic control should be less stringent. It is noteworthy that there are no hard data justifying either stringent or less stringent glycaemic control in this patient group.

ARGUMENTS FAVOURING LESS-TIGHT GLYCAEMIC CONTROL

Microvascular endpoints

Although the three landmark studies on intensive glycaemic control in people with long-standing diabetes [Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease (ADVANCE) and The Veterans Affairs Diabetes Trial (VADT)] included very few cases with advanced CKD, and even fewer frail older patients, these studies are the main source of evidence from which we can extrapolate data to frail older patients with advanced CKD. In these studies, microvascular hard endpoints such as the development of ESRD or doubling of the serum creatinine were not reduced by intensive glycaemic control in the initial reports [13–15]. These findings were further supported by a systematic review [12]. Although hard endpoints were unimproved in the short term, slight improvements in some were evident at later follow-up [33].

Cardiovascular endpoints and mortality

With regard to cardiovascular disease, the studies failed to demonstrate any benefit of intensive glucose control [13–15]. Moreover, the ACCORD study was prematurely stopped because of an unexpected 22% increase in the mortality rate in the intensive glycaemic control arm [13]. Similar data emerged from studies in older people as well as from observational studies in patients with CKD [8, 34–37]. Although there may be some absolute risk reductions in some surrogate vascular endpoints, more intense glycaemic therapy as applied in these trials cannot be justified when balanced against the risk of an increase in overall mortality [38]. Another finding that should moderate the temptation to implement more strict glycaemic control in patients with long-standing diabetes and comorbidities comes from a secondary analysis of the VADT trial. In this analysis, the only factors associated with new cardiovascular events were the presence of previous cardiovascular events and lower HbA_{1c} concentrations prior to the event [39]. This raises further concerns about the safety of intensive glycaemic control in patients with previous cardiovascular events or at risk of hypoglycaemia.

Cognitive impairment and depression

Cognitive impairment may represent an important outcome, since it is common in individuals with advanced CKD, with more than two-thirds of patients experiencing moderate to advanced cognitive impairment [40]. Likewise, patients with long-standing diabetes have a 1.5-fold increased risk of cognitive impairment and 2- to 4-fold increased risk of dementia [41]. In this regard, the results from the ACCORD and ADVANCE trials were disappointing, failing to provide any clinical benefit on cognitive function tests [14, 42]. These results do not support a strategy of tighter glycaemic control in frail older patients.

Depression may also be considered an important outcome since it is prevalent in individuals with diabetes, in advanced CKD and in older patients [43–45]. Moreover, depression is linked to mortality in patients with advanced CKD [46–48]. In patients with diabetes, depression confers strong risk of cognitive decline, cardiovascular events and mortality. Good glycaemic control did not improve its course [13, 49, 50]. These relationships are two-way since the burden of diabetes, CKD or frailty may lead to depressive symptoms, which may also be an important obstacle to achieving good glycaemic control [51, 52].

Hypoglycaemia and other health problems related to quality of life

The risk of severe hypoglycaemic events increases with age, glycaemic control, diabetes duration, progression of renal insufficiency and polypharmacy [53, 54]. Furthermore, hypoglycaemia may be aggravated by poor adherence and autonomic nervous dysfunction [55, 56]. In the VADT trial, hypoglycaemia was associated with an increased risk of cardiovascular events across all groups [39]. Hypoglycaemia increases the risk of falls [57–60] and fractures, decreasing independence and quality of life [61–63].

In older patients with diabetes and advanced CKD, maintaining independence and an acceptable quality of life may be more important than targeting a stringent HbA_{1c} level, with the intention of improving cardiovascular outcomes or medium- to long-term survival [64]. In these patients, quality of life is strongly associated with the burden of complex symptoms such as pain, pruritus, restless legs, nausea and fatigue. Alleviating these symptoms by treating anaemia or uraemia may be more effective in improving quality of life than strict glycaemic control [65]. Lack of independence, as well as polypharmacy, may have a great impact on quality of life [66, 67] (Figure 1).

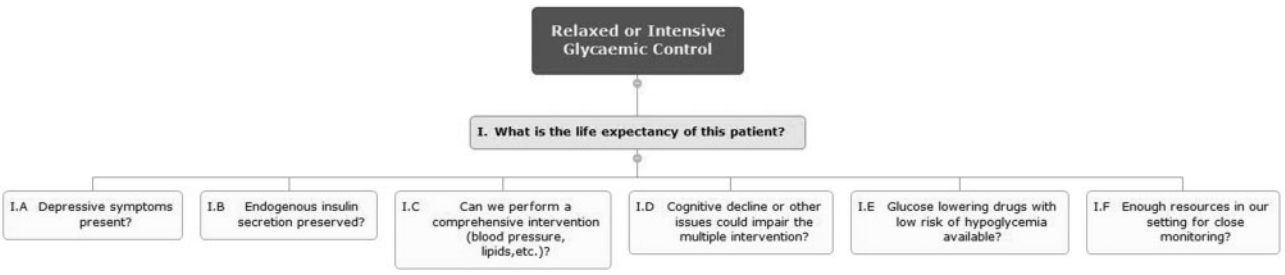

FIGURE 1: Factors to consider in the decision-making with regard to relaxed or intensive glycaemic control.

ARGUMENTS FAVOURING TIGHTER GLYCAEMIC CONTROL

The type of medication prescribed

When ACCORD, ADVANCE and VADT were performed, the only available glycaemia-lowering drugs were metformin, sulfonylureas, thiazolidinediones and insulins. Hence, in these studies many patients had regimes including sulfonylureas (50–71% of the patients) and/or insulin (40–87%) [68]. Both classes of agents exert their action independently of the blood glucose concentrations, having a continuous hypoglycaemic action and accordingly, a high risk for hypoglycaemia [53, 69]. More recently, the importance of postprandial glycaemic control in achieving better glycaemic control has been highlighted [70]. Older trials did not have the tools to adequately address both fasting and postprandial hyperglycaemia without conferring a high risk of hypoglycaemia. Now new classes of drugs have emerged that can safely address postprandial glycaemia. Some of these can be used in patients with advanced CKD [71]. These new drugs have shown acceptable safety profiles with respect to hypoglycaemia even in older patients [72]. Ongoing trials will determine whether use of these drugs confers any clinical benefit.

Microvascular endpoints

More intensive glycaemic control than currently recommended in older people with long diabetes duration also gains some support from signals of clinical benefit observed in the landmark trials. In the ADVANCE trial, the composite renal complications were reduced by 9%, mainly due to a 31% reduction in new onset macro-albuminuria, without increased mortality [73]. A later report from the same population showed a 65% reduction in the risk of progression to ESRD associated with intensive glycaemic control [33]. The absolute risk reduction was maximal in advanced CKD compared with the earlier stages [74]. A number of other defined renal outcomes were also reduced in ACCORD and VADT [15, 75]. The data also suggest that, in these respects, patients with type 2 diabetes and advanced CKD do not differ significantly from patients with type 2 diabetes without CKD.

Macrovascular endpoints

Although the initial reports of the VADT trial were negative, 10-year follow-up data demonstrated a 17% reduction in major cardiovascular events [76], although no reduction in overall mortality. The study population had a duration of diabetes of >10 years and a baseline HbA_{1c} of 9.5%. There were improvements in macrovascular outcomes after a period of intensive treatment for 5.6 years. The best achieved mean HbA_{1c} level was 6.9%, although this was followed by a small but persistent decline in the degree of glycaemic control [76]. It can be debated whether frail older people have sufficient life expectancy to benefit from these relatively small improvements.

Cognitive impairment and depression

Several studies have shown an association between higher glucose concentrations and worse cognitive performance, in both cross-sectional and retrospective analyses [77, 78]. In longitudinal observational studies, having diabetes seemed to enhance the effects of normal ageing by a factor of 1.5–2 over a period of 5 years [79–82]. Whether this effect is due to sustained hyperglycaemia or episodic hypoglycaemia is not clear. The beneficial effect of glycaemic control on cognitive function is supported by a randomized controlled trial that demonstrated a reduction in the rate of global cognitive decline after 5 years of improved glycaemic control [83, 84]. However, these studies focused primarily on the impact of telemedicine on HbA_{1c} control, and did not separately assess the role of tighter glycaemic control.

Time required to experience potential benefits

Even if there were some benefits of good glycaemic control, one might argue that many frail older people with advanced CKD may not survive long enough to experience the potential benefits of good glycaemic control. It appears that the benefits on microvascular disease may only emerge after 5 years or so in patients with long-standing diabetes and high cardiovascular risk, and that macrovascular benefits may need even longer follow-up [14, 15, 33, 75, 76, 85, 86]. Similar studies in older patients have shown that the time needed to observe benefits from tight glycaemic control in terms of microvascular complications was around 8 years [69]. In the diabetes population in general, there is a strong case for multiple and comprehensive interventions in patients with multiple risk factors [87]. The extent to which this applies to those who are old, frail and with advanced CKD needs to be carefully considered on an individual basis.

The new 'cardiovascular' glucose-lowering agents

Recent published data of randomized glucose-lowering agents showed cardiovascular and mortality benefits (e.g. EMPAREG Outcome trial, LEADER trial, SUSTAIN-6 trial) or kidney benefits (e.g. EMPAREG [88], ADVANCE-ON [86]) in patients with long-standing diabetes and high cardiovascular risk treated to achieve an HbA_{1c} of <7%. Whether the results can be generalized to older, frailer patients with advanced CKD is difficult to assess.

LEADER was an international, multicentred, randomized, double-blind, placebo-controlled trial comparing the safety and efficacy of the long-acting Glucagon-like peptide 1 receptor (GLP-1) agonist, liraglutide versus placebo in over 9340 people with type 2 diabetes mellitus and high cardiovascular risk [89]. More than 80% of participants had a history of previous cardiovascular disease. There was a reduction in rates of major cardiovascular events in patients randomized to liraglutide (13.0% versus 14.9%, respectively). The number needed to treat (NNT) to prevent one event over the 3-year period was 66 for major cardiovascular events and 98 for death from any cause. Liraglutide also reduced HbA_{1c}, body weight and incidence of hypoglycaemia. Its safety profile was similar to that seen in previous trials, with gastrointestinal adverse events and increases in heart rate being the most common. Only one-quarter of those randomized had an eGFR <60 mL/min/1.73 m^2. Mean age (± standard deviation) was 64.4 ± 7.2 years.

SUSTAIN-6 was a multicentred, international, randomized, double-blind, placebo-controlled trial, investigating the long-

Table 1. Summary of pros and cons of less-intensive glycaemic control in frail and older patients

Pros	Cons
There is a risk of increased mortality or at least no benefit	Clinical inertia may be exacerbated and lead to even higher mortality and morbidity
There is no benefit regarding cardiovascular disease in 5 years	There is a 17% reduction in macrovascular events after 10 years of follow-up There is a benefit regarding nephropathy progression
There is a 3- to 8-fold increase in hypoglycaemia	New drugs with low hypoglycaemic risk are available
There is a possible increased risk of cardiovascular events or mortality connected to hypoglycaemia	Hypoglycaemia is linked to cardiovascular events and mortality independent of intensive or conventional treatment
Cognitive dysfunction, depression and lack of independence could impair the effectiveness of educational programmes	Depression can be treated by other methods
This benefit of a more intensive glycaemic control appears after 5–8 years and this patient group has lower life expectancy	Comprehensive intervention targeting blood pressure, lipids, depression, along with glycaemic control benefits may result in greater benefits

term effects of semaglutide (0.5 and 1.0 mg), a long-acting GLP-1 receptor agonist, administered once weekly in adults with type 2 diabetes at high risk of cardiovascular events. In total, 3297 patients aged over 50 years (mean age 64.6 ± 7.4 years) with type 2 diabetes and an HbA_{1c} of 7% or more were randomized [90]. Of these, 2735 had established cardiovascular disease, CKD or both, but actual eGFRs were not provided; the remainder were aged at least 60 years with at least one cardiovascular risk factor. Mean duration of diabetes was 13.9 years and mean HbA_{1c} was 8.7%. Patients treated with semaglutide had a 26% lower risk of the primary composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke over 2 years compared with those receiving placebo. The NNT to prevent one event of the primary outcome over 2 years was 45.

The IDF recommends a restricted use of GLP-1 in the older population with or without CKD due to lack of long-term outcome and safety data in this specific population [91]. However, the recommendations are based on the information available in 2013, when the results of the recent trials mentioned above were not yet available. Their low potential for hypoglycaemia and availability for use as once a day or once a week make them seem attractive for use in older people. However, gastrointestinal side effects such as nausea and vomiting are common, which may not be appropriate for frail older people in whom weight loss and anorexia can be detrimental.

The multicentre Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME) randomized 7020 patients to daily empagliflozin (10 or 25 mg), a sodium–glucose cotransporter 2 inhibitor (SGLT2-I) or placebo [88]. At 3.1 years of follow-up, empagliflozin was associated with a reduction of a composite endpoint consisting of cardiovascular mortality, non-fatal myocardial infarction, or non-fatal stroke (10.5% versus 12.1%; $P = 0.04$), as well as a reduction in all-cause mortality (5.7% versus 8.3%; $P < 0.001$; NNT 38) and cardiovascular mortality (3.7% versus 5.9%; $P < 0.001$; NNT 45). Mean age of the included patients was 63.1 ± 8.6 years. Patients with eGFR <30 mL/min/1.73 m^2 were excluded from the trial, but around one-quarter of randomized patients had an eGFR between 30 and 60 mL/min/1.73 m^2. Although SGLT2 inhibitors have the advantage of low risk of hypoglycaemia and weight loss, their renal mode of action results in reduced efficacy in the presence of renal insufficiency. In addition, they can induce hypovolaemia and postural hypotension, further enhancing the risk of falls in an older population. They are also associated with an increased risk of genital and urinary tract infections. Taking all these into consideration, it can be stated that SGLT2 inhibitors are not really suitable drugs in older and frail patients with advanced CKD.

CONCLUSIONS

It is clear that intensive glycaemic control is not appropriate for many or even most frail older people with advanced CKD. Some subgroups may benefit from more intensive glycaemic control, such as those with a life expectancy of >5 years. In addition, if more intensive treatment is prescribed, it should be implemented with a medication that has a good safety profile and lower risk of hypoglycaemia (Table 1).

CONFLICT OF INTEREST STATEMENT

I.N. is a fellow of European Renal Best Practice (ERBP) and supported by a grant of the European Renal Association–European Dialysis Transplantation Association (ERA-EDTA). P.-H.G has received investigator-initiated research grants from Eli Lilly and Roche, is an Advisory Board Member for AbbVie, AstraZeneca, Boehringer-Ingelheim, Cebix, Eli Lilly, Janssen, Medscape, Novartis, Novo Nordisk and Sanofi, and has received lecture honorariums from Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, Genzyme, MSD, Novartis, Novo Nordisk and Sanofi. No other potential conflicts of interest relevant to this article were reported. N.M.P. has received lecture fees from Eli Lilly. W.V.B. is chair of ERBP and has no conflict regarding the topics handled in this manuscript. The results presented in this article have not been published previously in whole or part, except in abstract format.

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Received: 26.9.2016; Editorial decision: 24.1.2017